IN THE SPECIFICATION

Please amend the specification as provided below:

1. Please replace the paragraph beginning on page 2, line 23, with the following rewritten paragraph:

-- Patients with significant physiologic stress are at risk for stress-related gastric mucosal damage and subsequent upper gastrointestinal bleeding (Marrone and Silen, *Pathogenesis, Diagnosis and Treatment of Acute Gastric Mucosa Lesions,* CLIN GASTROENTEROL 13: 635-650 (1984)). Risk factors that have been clearly associated with the development of stress-related mucosal damage are mechanical ventilation, coagulopathy, extensive burns, head injury, and organ transplant (Zinner et al., *The Prevention of Gastrointestinal Tract Bleeding in Patients in an Intensive Care Unit,* SURG. GYNECOL. OBSTET., 153: 214-220 (1981); Larson et al., *Gastric Response to Severe Head Injury,* AM. J. SURG. 147: 97-105 (1984); Czaja et al., *Acute Gastroduodenal Disease After Thermal Injury: An Endoscopic Evaluation of Incidence and Natural History,* N ENGL. J. MED, 291: 925-929 (1974); Skillman et al., *Respiratory Failure, Hypotension, Sepsis and Jaundice: A Clinical Syndrome Associated with Lethal Hemorrhage From Acute Stress Ulceration,* AM. J. SURG., 117: 523-530 (1969); and Cook et al., *Risk Factors for Gastrointestinal Bleeding in Critically Ill Patients,* N. ENGL. J. MED., 330:377-381 (1994)). One or more of these factors are often found in critically ill, intensive care unit patients. A recent cohort study challenges other risk factors previously identified such as acid-base disorders, multiple trauma, significant hypertension, major surgery, multiple operative procedures, acute renal failure, sepsis, and coma (Cook et al., *Risk Factors for Gastrointestinal Bleeding in Critically Ill Patients,* N. ENGL. J. MED., 330:377-381 (1994)). Regardless of the risk type, stress-related mucosal damage results in significant morbidity and mortality.

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Clinically significant bleeding occurs in at least twenty percent of patients with one or more risk factors who are left untreated (Martin et al., *Continuous Intravenous Cimetidine Decreases Stress-related Upper Gastro-intestinal Hemorrhage Without Promoting Pneumonia,* CRIT. CARE MED., 21: 19-30 (1993)). Of those who bleed, approximately ten percent require surgery (usually gastrectomy) with a reported mortality of thirty percent to fifty percent (Czaja et al., *Acute Gastroduodenal Disease After Thermal Injury: An Endoscopic Evaluation of Incidence and Natural History,* N ENGL. J. MED, 291: 925-929 (1974); Peura and Johnson, *Cimetidine for Prevention and Treatment of Gastroduodenal Mucosal Lesions in Patients in an Intensive Care Unit,* ANN INTERN MED., 103: 173-177 (1985)). Those who do not need surgery often require multiple transfusions and prolonged hospitalization. Prevention of stress-related upper gastrointestinal bleeding is an important clinical goal.--

2. Please replace the paragraph beginning on page 4, line 10, with the following rewritten paragraph:

--In addition to general supportive care, the use of drugs to prevent stress-related mucosal damage and related complications is considered by many to be the standard of care (AMA Drug Evaluations). However, general consensus is lacking about which drugs to use in this setting (Martin et al., *Continuous Intravenous Cimetidine Decreases Stress-related Upper Gastrointestinal Hemorrhage Without Promoting Pneumonia,* CRIT. CARE MED., 21: 19-30 (1993); Gafter et al., *Thrombocytopenia Associated With Hypersensitivity to Ranitidine: Possible Cross-reactivity with Cimetidine,* AM. J. GASTROENTEROL, 84: 560-562 (1989); Martin et al., *Stress Ulcers and Organ Failure in Intubated Patients in Surgical Intensive Care Units,* ANN SURG., 215: 332-337 (1992)). In two recent meta-analyses (Cook et al., *Stress Ulcer Prophylaxis in the Critically Ill: A Meta-analysis,* AM. J. MED., 91: 519-527 (1991); Tryba, *Stress Ulcer*

Prophylaxis - Quo Vadis? INTENS. CARE MED. 20: 311-313 (1994)) antacids, sucralfate, and H_2-antagonists were all found to be superior to placebo and similar to one another in preventing upper gastrointestinal bleeding. Yet, prophylactic agents are withdrawn in fifteen to twenty percent of patients in which they are employed because of failure to prevent bleeding or control pH (Ostro et al., *Control of Gastric pH With Cimetidine Boluses Versus Primed Infusions,* GASTROENTEROLOGY, 89: 532-537 (1985); Siepler, *A Dosage Alternative for H-2 Receptor Antagonists, Continuous-Infusion,* CLIN. THER., 8(SUPPL A): 24-33 (1986); Ballesteros et al., *Bolus or Intravenous Infusion of Ranitidine: Effects on Gastric pH and Acid Secretion: A Comparison of Relative Cost and Efficacy,* ANN. INTERN. MED., 112:334-339 (1990)), or because of adverse effects (Gafter et al., *Thrombocytopenia Associated With Hypersensitivity to Ranitidine: Possible Cross-reactivity With Cimetidine,* AM. J. GASTROENTEROL, 84: 560-562 (1989); Sax, *Clinically Important Adverse Effects and Drug Interactions With H2-Receptor Antagonists: An Update,* PHARMACOTHERAPY 7(6 PT 2): 110S-115S (1987); Vial et al., *Side Effects of Ranitidine,* DRUG SAF, 6:94-117(1991); Cantu and Korek, *Central Nervous System Reactions to Histamine-2 Receptor Blockers,* ANN. INTERN MED., 114: 1027-1034 (1991); and Spychal and Wickham, *Thrombocytopenia Associated With Ranitidine,* BR. MED. J., 291: 1687 (1985)). In addition, the characteristics of an ideal agent for the prophylaxis of stress gastritis were analyzed by Smythe and Zarowitz, *Changing Perspectives of Stress Gastritis Prophylaxis,* ANN PHARMACOTHER, 28: 1073-1084 (1994) who concluded that none of the agents currently in use fulfill their criteria.--

3. Please replace the paragraph beginning on page 20, line 7, with the following rewritten paragraph:

-- Second, because bicarbonate is usually neutralized in the stomach or is absorbed, such that belching results, patients with gastroesophageal reflux may exacerbate or worsen their reflux disease as the belching can cause upward movement of stomach acid (Goodman AG, et al., *Agents for the Control of Gastric Acidity and Treatment of Peptic Ulcers*, in, THE PHARMACOLOGIC BASIS OF THERAPEUTICS (New York, p. 907 (1990)).--

4. Please replace the paragraph beginning on page 29, line 22, with the following rewritten paragraph:

-- The liquid oral pharmaceutical composition of the present invention is prepared by mixing omeprazole (Prilosec® AstraZeneca) or other proton pump inhibitor or derivatives thereof with a solution including at least one buffering agent (with or without a parietal cell activator, as discussed below). Preferably, omeprazole or other proton pump inhibitors, which can be obtained from a capsule or tablet or obtained from the solution for parenteral administration, is mixed with a sodium bicarbonate solution to achieve a desired final omeprazole (or other PPI) concentration. As an example, the concentration of omeprazole in the solution can range from approximately 0.4 mg/ml to approximately 10.0 mg/ml. The preferred concentration for the omeprazole in the solution ranges from approximately 1.0 mg/ml to approximately 4.0 mg/ml, with 2.0 mg/ml being the standard concentration. For lansoprazole (Prevacid® TAP Pharmaceuticals, Inc.) the concentration can range from about 0.3 mg/ml to 10 mg/ml with the preferred concentration being about 3 mg/ml.--

5. Please replace the paragraph beginning on page 51, line 4, with the following rewritten paragraph:

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-- Children are affected by gastroesophageal reflux disease (GERD) with atypical manifestations. Many of these atypical symptoms are difficult to control with traditional drugs such as H_2-antagonists, cisapride, or sucralfate. PPIs are more effective in controlling gastric pH and the symptoms of GERD than other agents. However, PPIs are not available in dosage forms that are easy to administer to young children. To address this problem, applicant employed omeprazole or lansoprazole in a buffered chocolate suspension (Choco-Base™) in children with manifestations of GERD.--

6. Please replace the paragraph beginning on page 52, line 30, with the following rewritten paragraph:

-- Applicant performed a retrospective evaluation of children with GERD referred to the University of Missouri-Columbia from 1995 to 1998 who received treatment with the experimental omeprazole or lansoprazole Choco-Base™ suspension formulated in accordance with Formulation 1 stated below. Data were included on all patients with follow up information sufficient to draw conclusions about pre/post treatment (usually > 6 months). There were 25 patients who met the criteria for this evaluation. Age range was several weeks to greater than 5 years. Most patients had a history of numerous unsuccessful attempts at ameliorating the effects of GERD. Medication histories indicated many trials of various drugs.--

NE 7. Please replace the paragraph beginning on page 52, line 30, with the following rewritten paragraph:

--Of the 24 remaining patients, 18 were males and 6 were females. Ages at implementation of PPI therapy ranged from 2 weeks of age to 9 years old. Median age at start of therapy was 26.5 months [mean of 37 mo.] Early on, reflux was usually documented by

endoscopy and confirmed by pH probe. Eventually, pH probe was dropped and endoscopy was the sole method for documenting reflux, usually at the time of another surgery (most often T-tubes or adenoidectomy). Seven patients had pH probe confirmation of GERD, whereas 18 had endoscopic confirmation of reflux including all eight who had pH probing done (See Graphs 1 and 2 below). Reflux was diagnosed on endoscopy most commonly by cobblestoning of the tracheal wall, with laryngeal and pharyngeal cobblestoning as findings in a few patients. Six patients had neither pH nor endoscopic documentation of GERD, but were tried on PPI therapy based on symptomatology alone.--

8. Please replace the paragraph beginning on page 55, line 3, with the following rewritten paragraph:

-- Most patients responded favorably to and tolerated the once daily dosing of Choco-Base™ proton pump inhibitor suspension. Two patients had documented adverse effects associated with the use of the PPI suspension. In one patient, the mother reported increased burping up and dyspepsia, which was thought to be related to treatment failure. The other patient had small amounts of bloody stools per mother. This patient never had his stool tested, as his bloody stool promptly resolved upon cessation of therapy, with no further sequellae. The other 23 patients had no documented adverse effects.--

9. Please replace the paragraph beginning on page 64, line 3, with the following rewritten paragraph:

-- In all four of the above formulations, lansoprazole or other PPI can be substituted for omeprazole in equipotent amounts. For example, 300 mg of lansoprazole may be substituted for the 200 mg of omeprazole. Additionally, aspartame can be substituted for sucrose, and the

following other ingredients can be employed as carriers, adjuvants and excipients: maltodextrin, vanilla, carragreenan, mono and diglycerides, and lactated monoglycerides. One skilled in the art will appreciate that not all of the ingredients are necessary to create a Choco-Base™ formulation that is safe and effective.--

10. Please replace the paragraph beginning on page 65, line 8, with the following rewritten paragraph:

--Applicant additionally analyzed the effects of a lansoprazole Choco-Base™ formulation on gastric pH using a pH meter (Fisher Scientific) in one adult patient versus lansoprazole alone. The patient was first given a 30 mg oral capsule of Prevacid®, and the patient's gastric pH was measured at 0, 4, 8, 12, and 16 hours post dose. The results are illustrated in Fig. 4.--

11. Please replace the paragraph beginning on page 65, line 15, with the following rewritten paragraph:

-- The Choco-Base product was compounded according to Formulation 1 above, except 300 mg of lansoprazole was used instead of omeprazole. A dose of 30 mg lansoprazole Choco-Base™ was orally administered at hour 18 post lansoprazole alone. Gastric pH was measured using a pH meter at hours 18, 19, 24, 28, 32, 36, 40, 48, 52, and 56 post lansoprazole alone dose.--

12. Please replace Table 4 on page 83, with the following Table 4:

--TABLE 4

he average length of treatment was 9 days. Cost of care was calculated from these days.

	Per Day	Total

)MEPRAZOLE (day 1)			
'roduct acquisition cost	40 mg load x 2 5.66/dose)	11.32	11.32
ıncillary product	materials for solution preparation	0.41	0.41
ıncillary product	syringe w/needle	0.20	0.40
:terile preparation required	no		
:OS preparation time (R.N.)	6 minutes	2.40	4.80
:.N. time ($24/hr)	21 minutes/day (includes pH monitoring)	8.40	8.40
)MEPRAZOLE (days 2-9)			
'roduct acquisition cost	20 mg per day	2.80	22.65
ıncillary product	materials for solution preparation	0.41	0.82
ıncillary product	syringe w/needle	0.20	1.60
:terile preparation required	no		
:OS preparation time (R.N.)	6 minutes	2.40	4.80
:.N. time ($24/hr)	18 minutes/day (includes pH monitoring)	8.40	57.60
/75 patient require 40 mg simplified omeprazole solution per day (days 2-9)			0.63
Jo additional cost for adverse effects or for failure			
'OTAL□	113.43		
:implified Omeprazole Solution cost per day □	12.60		

Pharmacoeconomic evaluation of omeprazole cost of care--

13. Please replace Table 5 on page 83, with the following Table 5:

TABLE 5

'ime	Control	1 hour	24 hour	2 day	7 day	14 day
:onc (mg/ml)	2.01	2.07	1.94	1.96	1.97	1.98

tability of Simplified Omeprazole Solution at room temperature
25° C.). Values are the mean of three samples.—

14. Please replace the paragraph beginning on page 84, line 21, with the following rewritten paragraph:

--(b) 20 mg of a liquid formulation of approximately 2 mg omeprazole per 1 ml of 8.4% sodium bicarbonate;--

15. Please replace the paragraph beginning on page 86, line 16, with the following rewritten paragraph:

-- Blood samples will be centrifuged within 2 hours of collection and the plasma will then be separated and frozen at –10° C (or lower) until assayed. Pharmacokinetic variables will include: time to peak concentration, mean peak concentration, AUC (0-t) and (0-infinity). Analysis of variance will be used to detect statistical difference. Bioavailability will be assessed by the 90% confidence interval of the two one-sided tests on the natural logarithm of AUC.—

16. Please replace the paragraph beginning on page 86, line 26, with the following rewritten paragraph:

-- Omeprazole and internal standard (H168/24) will be used. Omeprazole and internal standard will be measured by modification of the procedure described by Amantea and Narang. (Amantea MA, Narang PK. Improved Procedure for Quantification of Omeprazole and Metabolites Using Reversed-Phased High Performance Liquid Chromotography. J. CHROMATOGRAPHY 426; 216-222. 1988). Briefly, 20□l of omeprazole 2mg/ml $NaHCO_3$ or Choco-Base™ omeprazole suspension and 100□l of the internal standard are vortexed with 150 µl of carbonate buffer (pH=9.8), 5 ml of dichloromethane, 5 ml of hexane, and 980 µl of sterile water. After the sample is centrifuged, the organic layer is extracted and dried over a nitrogen stream. Each pellet is reconstituted with 150 µl of mobile phase (40% methanol, 52% 0.025 phosphate buffer, 8% acetonitrile, pH=7.4). Of the reconstituted sample, 75 µl is injected onto a C18 5 U column equilibrated with the same mobile phase at 1.1ml/min. Under these conditions, omeprazole is eluted at approximately 5 minutes, and the internal standard at approximately 7.5 minutes. The standard curve is linear over the concentration range 0-3 mg/ml (in previous work with SOS), and the between-day coefficient of variation has been <8% at all concentrations. The typical mean R2 for the standard curve has been 0.98 in prior work with SOS (omeprazole 2mg/ml NaHCO3 8.4%).--

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17. Please replace the paragraph beginning on page 89, line 6, with the following rewritten paragraph:

-- A solution was prepared by mixing 8.4% sodium bicarbonate with omeprazole to produce a final concentration of 2 mg/ml to determine the stability of omeprazole solution after 12 months. The resultant preparation was stored in clear glass at room temperature, refrigerated and frozen. Samples were drawn after thorough agitation from the stored preparations at the prescribed times. The samples were then stored at 70°C. Frozen samples remained frozen until they were analyzed. When the collection process was completed, the samples were shipped to a laboratory overnight on dry ice for analysis. Samples were agitated for 30 seconds and sample aliquots were analyzed by HPLC in triplicate according to well known methods. Omeprazole and the internal standard were measured by a modification of the procedure described by Amantea and Narang. Amantea MA, Narang PK, Improved Procedure For Quantitation Of Omeprazole And Metabolites Using Reverse-Phased High-Performance Liquid Chromatography, J. Chromatography, 426: 216-222 (1988). Twenty (20) μl of the omeprazole 2mg/ml $NaHCO_3$ solution and 100 μl of the internal standard solution were vortexed with 150 μl of carbonate buffer (pH = 9.8), 5 ml dichloromethane, 5 ml hexane, and 980 μl of sterile water. The sample was centrifuged and the organic layer was extracted and dried over a nitrogen stream. Each pellet was reconstituted with 150 μl of mobile phase (40% methanol, 52% 0.025 phosphate buffer, 8% acetonitrile, pH=7.4). Of the reconstituted sample, 75 μl were injected onto a C185u column equilibrated with the same mobile phase at 1.1 ml/min. Omeprazole was eluted at ~5 min, and the internal standard at ~7.5 min. The standard curve was linear over the concentrated range 0-3 mg/ml, and between-day coefficient of variation was < 8% at all concentrations. Mean R2 for the standard curve was 0.980.--